REMARKS

To advance prosecution, the Applicants herewith amend the title to recite "RECEPTOR REGULATOR CONTAINING A NITROGEN-CONTAINING RING DERIVATIVE HAVING AN AMINO GROUP." Support for the title is found *inter alia*, at page 1, lines 4-6 of the specification.

Claim 11 now incorporates the subject matter of claim 25. Claim 25 is cancelled. Claims 1-10, 24 and 27 are cancelled without prejudice or disclaimer. Claims 16, 18 and 20 are amended to be consistent with the amendment to claim 11. Claim 28 is amended to delete the recitation of "a prodrug thereof." Claim 29 is added. Support for claim 29 is found, *inter alia*, at the paragraph bridging pages 72 and 73 of the specification. No new matter is added. Entry of the Amendment is respectfully requested.

Upon entry of the Amendment, claims 11-23, 26 and 28-29 will be pending, of which claims 18 and 19 are withdrawn from consideration.

I. Claim to Foreign Priority

Applicants respectfully request acknowledgement of Applicants' claim to foreign priority and acknowledgement that the certified copy of the priority document has been received.

II. The Title is Proper

At page 4 of the Office Action, the title is objected to because it is allegedly "not descriptive." In order to compact prosecution, Applicants herewith amend the title.

Withdrawal of the objection to the title is therefore requested.

III. Claim 1 is Proper

At page 5 of the Office Action, Claim 1 is objected because the phrase "nitrogen-containing" occurs twice at line 4 of claim 1.

Claim 1 is been cancelled thus the objection is moot.

IV. Claims 1-8, 11-17, 20-26 and 28 Are Enabled and Definite Under 35 U.S.C. § 112

At page 5 of the Office Action, claims 1-8, 11-17, 20-26 and 28 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. At page 6 of the Office Action, claims 1-8, 11-17, 20-26 and 28 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement for the term "prodrugs." At page 7 of the Office Action, claims 1-8, 11-17, 20-26 and 28 are rejected under 35 U.S.C. § 112, first paragraph, as not enabled with respect to the claimed substituents being "optionally substituted."

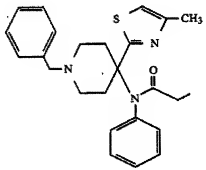
Applicants herewith amend the claims without prejudice or disclaimer. Applicants' amendments overcome the rejections.

Withdrawal of the § 112 rejections is requested.

V. Claims 1-8, 11-17, 20-26 and 28 Are Novel Under 35 U.S.C. §§ 102(b) and 103

At page 12 of the Office Action, claims 1-8, 11-17, 20-26 and 28 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Lin *et al.* (US Patent No. 4,871,749 A and US Patent No. 4,791,120 A).

The Examiner asserts that Lin *et al.* discloses compounds and compositions of Formula I'''' wherein R2b=ethyl, R1b= 4-methyl-2-thiazolyl, Z1=CH2 and R3=phenyl (see Example 3, column 10, shown below).



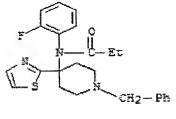
However, the compound cited by the Examiner from Lin *et al.* '749 and '120 is explicitly excluded from the claimed subject matter. For this reason, Lin *et al.* does not disclose or render obvious the present invention.

In view of the above, reconsideration and withdrawal of the §102(b) rejection based on Lin *et al.* are requested.

At page 13 of the Office Action, claims 1-8, 11-17, 20-26 and 28 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Kudzma *et al.* (J. Med. Chem., 1989, 32, 2534-42).

Applicants submit that this rejection should be withdrawn because Kudzma *et al.* does not disclose or render obvious the present invention.

The Examiner refers to compound 8e, page 2535, scheme 1 (shown below) of Kudzma *et al.*, which corresponds to formula I'''' wherein R2b=ethyl, R1b= 2-thiazolyl, Z1=CH2 and R3=phenyl.

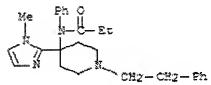


However, the compound cited by the Examiner from Kudzma *et al.* is explicitly excluded from the claimed subject matter and therefore cannot anticipate the claims.

In view of the above, reconsideration and withdrawal of the §102(b) rejection based on Kudzma *et al.* are requested.

At page 14 of the Office Action, claims 1-8, 11-17, 20-26 and 28 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Lin *et al.* (US Patent No. 4,831,192 A).

According to the Examiner, the Lin *et al.* '192 reference renders obvious the invention recited in claims 1-8, 11-17, 20-26 and 28 because Lin *et al.* '192 discloses compounds and compositions of Formula I'''' wherein R2b=ethyl, R1b= 1-methyl-2-imidiazol-2-yl, Z1= CH2CH2 and R3=phenyl (see Compound 1, column 45/46, shown below).



The Examiner asserts that Lin *et al.* differs from the instant invention at the -Z1R3 position where Lin *et al.* discloses -CH2CH2-phenyl and Applicants disclose -CH2-phenyl. However, the Examiner alleged it would have been obvious to reduce the alkylene linker from -CH2CH2- to -CH2-.

Applicants respectfully disagree.

A corresponding compound of the formula (I'''') wherein Z1 is methylene whose representative example is Fentanyl is known to act on an opioid receptor with morphine, and to have analgesic activity.

In contrast, in synthetic processes, a benzyl group (Z1 = methylene) is widely used as a protective group of an amine and, in Kudzma *et al.*, compounds 8d-8k are synthesized as intermediates. Their biological activities are undisclosed and they do not have opioid activity. They are formed as mere intermediates. The law is clear that when the alleged prior art does not teach a specific or significant utility for the disclosed compounds, the art cannot render structurally similar claims prima facie obvious because there is no motivation for one of ordinary skill in the art to make the reference compounds, much less structurally related compounds. See MPEP § 2144.09 and *In re Stemniski*, 444 F.2d 581, 170 USPQ 343 (CCPA 1971). In order to prove obviousness based on structural similarity between a claimed invention and the cited prior art, it is necessary to demonstrate that a reason or motivation to make the claimed compositions is indicated in the prior art reference. *In re Dillon*, 919 F.2d, 688 (Fed. Cir. 1990). No reason or motivation is set forth. It is also necessary to demonstrate that there exists adequate support in the cited reference for the necessary change in structure. *In re Grabiak*, 769 F.2d 729, 731-32 (Fed. Cir. 1985). No support in the reference as cited by the Examiner refers to support for the necessary change in chemical structure.

The Examiner further fails to state a reason that would have prompted a person of ordinary skill in the art relevant field to obtain Applicants' claimed compound from the compound disclosed in the cited reference because the prior art indicates, "compounds of the present invention possess potent analgesic and anesthetic properties." Lin et al., column 1, lines 33-34. The Applicants discovered that the compound of the formula (I'''') wherein Z1 is methylene has neuromedin receptor function regulating activity and is useful as a medicament. At paragraph 180 of Applicants' specification, the Applicants teach, "...the compound of the

present invention can be used as a preventive/therapeutic agent for hypertension, cardiac infarct, acute renal dysfunction, or stress disease (e.g. (i) cardiac vascular disease (angina, cardiac infarct, arrhythmia etc.), (ii) respiratory disease (bronchial asthma, hyperpnea syndrome etc.), (iii) muscular skeletal disease (rheumatoid arthritis, lumbago, migraine, tension headache etc.), (iv) others (diabetes, climacteric disorder, chronic pain, immune activity reduction etc.)), or a digestive tract disease (stomach ulcer, ulcerative colitis etc.)." The Examiner's position is therefore inconsistent with precedent which indicates that a rationale must be set forth to support a charge of obviousness. *KSR International Co. v. Teleflex, Inc.*, 550 U.S. ____ (2007). There is no articulated or logical rationale for compounds having analgesic and anesthetic properties rendering obvious Applicants' compounds directed to, for example, hypertension, cardiac infarct or acute renal dysfunction. Lin et al. further indicate that the observed ED_{50} of the compound cited by the Examiner in no way prompts a person of ordinary skill in the art relevant field to obtain Applicants' claimed compound from the corresponding compound cited in the reference because the endpoint falls within many compounds having greater or less values.

Therefore, it is clear that the corresponding compound disclosed in Lin *et al* wherein Z1 is ethylene does not teach or suggest the compound of the present invention and therefore cannot possibly render obvious Applicants' invention.

In view of the above, reconsideration and withdrawal of the §103(a) rejection based on Lin *et al.* are respectfully requested.

Allowance is respectfully requested. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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